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## The Classic

### Registry of Bone Sarcoma: Part I.—Twenty-Five Criteria for Establishing the Diagnosis of Osteogenic Sarcoma. Part II.—Thirteen Registered Cases of “Five Year Cures” Analyzed According to These Criteria

Ernest Amory Codman MD

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**Abstract** This Classic Article is a reprint of the original work by Ernest Amory Codman, Registry of Bone Sarcoma: Part I.—Twenty-Five Criteria for Establishing the Diagnosis of Osteogenic Sarcoma. Part II.—Thirteen Registered Cases of “Five Year Cures” Analyzed According to These Criteria. An accompanying biographical sketch of Ernest Amory Codman, MD, and The Classic: The Registry of Bone Sarcomas as an Example of the End-Result Idea in Hospital Organization are available at DOIs [10.1007/s11999-009-1047-8](https://doi.org/10.1007/s11999-009-1047-8) and [10.1007/s11999-009-1048-7](https://doi.org/10.1007/s11999-009-1048-7), respectively. The Classic Article is ©1926 by the Journal of the American College of Surgeons and is

reprinted with permission from Codman EA. Registry of bone sarcoma; part I, twenty-five criteria for establishing diagnosis of osteogenic sarcoma; part II, 13 registered cases of 5 year cures analyzed according to these criteria. *Surg Gynecol Obstet.* 1926;42:381–393.

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Richard A. Brand MD (✉)  
Clinical Orthopaedics and Related Research, 1600 Spruce Street,  
Philadelphia, PA 19103, USA  
e-mail: dick.brand@clinorthop.org

## Introduction

One of the primary objects of the registry was to keep an up-to-date list of living cases which had had bone sarcoma and which could be considered as cured. It should be remembered that the Registry was started for and by the family of a patient under the care of the writer for a supposed bone sarcoma. They wished and I wished to ascertain the actual facts as to whether there were any living cured cases of this disease and if there actually were, to ascertain the methods of treatment by which these patients had been cured. I was given a thousand dollars to pay my expenses in obtaining the required facts.

My first step (in August, 1920) was to address a circular letter to the individual members of the American College of Surgeons and to the surgical profession in general. The advice of Dr. Ewing and Dr. Bloodgood was sought in consultation. Through the kindness of my personal friends in several earnest clinics, follow-up investigations were

started. In fact that gift of a thousand dollars made me and many others work and soon led the Regents of the College to add an aggregate of \$8000 more, contributed from time to time, in order to answer these two simple questions. Now at the end of five years, only 17 cases of primary malignant bone tumors have been collected which in our opinion may be considered cured (Ewing's tumor, 4 cases—osteogenic sarcoma, 13 cases).

In spite of all our efforts my patient died within the year and autopsy showed that the supposed sarcoma was a metastatic cancer of unknown origin. The chagrin of the error in diagnosis was somewhat allayed when reports from various clinics stimulated by our investigation began to appear. Greenough, Simmons, and Harmer analyzing the cases from the Massachusetts General Hospital and Huntington Memorial Hospital, for instance, reported: “Perhaps the most surprising fact of the whole study is that of 148 cases, sent in as possible bone sarcoma, only 68 could be considered in fact to be cases of malignant

newgrowth of bony origin; the remaining 82 cases proving on more detailed study to be metastatic tumors of bone (29 cases), sarcoma primary in the soft parts (28 cases), inflammatory conditions (11 cases), or tumors of a non-sarcomatous type (14 cases)."

It soon appeared that by-products were to be the result of our industry rather than the intended product of obtaining the answers to our simple questions. The Registry itself was a by-product, for when our collection of cases could no longer be of possible benefit to my patient the Regents saw that the same questions would be eternal. The friends of future patients would always want to know of the living cases and how they were cured. Five years have passed since the first circular letter went out and some of our by-products may be listed as follows:

1. Many contributions to the medical literature on bone tumors.
2. A more or less acceptable standard classification, presented and discussed in the form of a small book. (Reprinted in Bull. Am. Col. of Surg., 1926, x, No. 1, A.)
3. The impersonal proof of Dr. Bloodgood's contention that giant cell tumor is benign.
4. The impersonal proof that cases of giant cell tumor may be cured by radiotherapy.
5. The diffusion of Dr. Mallory's contention that benign giant cell tumor is not a neoplasm but a faulty repair phenomenon.
6. The impersonal proof that many of the cures from combined treatment by surgery, mixed toxins, and radium claimed by Dr. Coley are authentic.
7. The principle of co-operative education (concerning rare diseases) among laboratories (the founding of other Registries).
8. The possession by the American College of Surgeons of collections of data on 100 standard benign giant cell tumors, 100 standard osteogenic sarcomata of the femur, 100 standard osteogenic sarcomata of other bones, 50 standard cases of Ewing's tumor. (These data are neatly packed in trunk-like boxes available for study by investigators or by pathologists or surgeons who see few bone tumor cases but who occasionally must decide questions of life and limb.)
9. A principle suggested for the new Museum of the College (and for other museums) of accumulation of data on accepted standard clinical entities, in available form for intensive research and educational study.
10. The idea that the Museum might become a sort of patent office of new clinical entities. A practical example of this idea by submitting a collection of over 50 cases of Ewing's tumor.

11. The suggestion that the College should devote its energies to the standardization of series of surgical cases, asking from hospitals duplicate records of one series after another. (For instance, a check on the standardization of hospitals might be made in epitome on the manner in which the cases of bone sarcoma are registered since such registration tests not only the apparatus of roentgenologist, pathologist, and surgeon, but the education, cerebration, and practical efficiency of the staff and perhaps even their consciences.)

There are other by-products, but the true product of our industry is small—only 17 cases of 5 year cures of primary, malignant tumors of bone on which the Committee can agree even tentatively. And in these cases much essential evidence is lacking. In ten of these for instance the X-ray has been lost. The evidence on few of the 17 is entirely convincing.

As to the treatment, all but 1 of the 17 had amputation and that one had a local exploration followed by intensive radium treatment and mixed toxins. Nine of the other 16 also had toxins. Eight also had radiation. In 8 cases these treatments were combined. Seven had no other treatment than amputation so far as we know.

I think the average surgeon will perhaps be content with the two paragraphs above. He will continue to amputate in doubtful cases if he thinks there is any possible chance that no metastases have already occurred. He will ignore the fact that the one radium and toxin cure probably represents a greater percentage of cures among those where this combination of treatments has been attempted than the sixteen amputations represent to the vast number in which surgery has failed.

We have many unknown factors: (1) How many amputations have been done and failed? (2) How many cases have there been in which the mixed toxins have been *thoroughly tried* and failed with or without amputation? (3) How many cases have received *thorough* radiation with or without surgery.

We have few facts and can estimate as we please. The answers are probably: (1) Very, very many. (2) A good many. (3) Very few or even very, very few. And all this guesswork must take into consideration that of all the cases submitted to the Registry as sarcomata, the Committee believes only a little over 50 per cent were actually malignant primary tumors of bone!

Since the Registry was not quite 5 years old at the time this set of 17 cases was agreed on by the Committee (June 1, 1925), the real use of the collection in answering our question will not be attained for 5 years from that date. It can then deal with cases of standard diagnoses agreed on before the result is known. *At present we can only say that*

*it is probable that an occasional case may be saved by amputation or by amputation combined with toxins and radium; and that in 1 atypical case of primary malignant bone tumor with metastasis in the groin the patient recovered after an exploratory operation and the postoperative use of Coley toxins and radium.*

Will the reader please reconsider the last sentence and bear in mind that these statements were made by the Registrar of a Committee of the largest surgical society in the world consisting of over 7,000 members, every one of whom has been repeatedly solicited to register any case of bone sarcoma in which the patient is living, whether cured, under treatment, or moribund, and especially if cured 5 years ago!

And yet anyone in searching the literature will find many reports of cures and percentages of cures. Read again the above quotation from Greenough, Simmons, and Harmer, and reflect on the percentage of erroneous diagnoses compared with the percentage of cures.

However, the paragraph in italics does not give all our optimism for it is boiled down to the coldest hardest facts. We have other evidence that all of these therapeutic agents, amputation, Coley toxins, and radium are effective in greater or less degree. There are a few more cases remaining well 5 years which we *almost* accept. There are many 5 year cures in cases which we consider benign giant cell tumor and a considerable number of cases of osteogenic sarcoma are nearing the 5 year limit. We are confident that each year in the future the report of the Registrar will be more favorable—particularly in regard to the use of radiation.

The Committee of which I was Registrar will be abundantly satisfied if they have succeeded in establishing a moderately acceptable standard nomenclature and moderately acceptable criteria of malignancy. To recommend an absolute nomenclature or absolute criteria would be ridiculous. Nevertheless, nomenclature and criteria must precede statistics on therapeutics.

### **Part I.—Twenty-Five Criteria for Establishing the Diagnosis of Osteogenic Sarcoma**

Our list of 17 cured cases applies only to primary malignant tumors of bone, that is, to our classes of osteogenic sarcoma (13) and of Ewing's tumor (4). Of the latter I shall say little because there is at this writing an article in press for the *Archives of Surgery*, by C. L. Conner which analyzes all our cases of Ewing's tumor and really gives the most up-to-date knowledge of this new entity. The four 5 year cures of Ewing's tumor No. 185, No. 267, No. 348, No. 398 will there be reported. They will also be reported from the Memorial Hospital Clinic of New York by Coley

and some have already appeared in the literature in Ewing's articles. As will appear in Conner's critical analysis, Ewing's tumor is in a class by itself as far as prognosis under radiation is concerned. It was this favorable response to radiation which first led Ewing to see that it was a separate entity apart from true osteogenic sarcoma.

Before speaking individually of the 13 remaining cases of supposed 5 year cures, let us consider the criteria of malignancy in osteogenic sarcoma. Out and out cases of malignant osteogenic sarcoma will show every one of these points, although occasionally one or two may be doubtful, absent, or impossible to verify (Table 1).

### **History**

Nearly all histories of osteogenic sarcoma cases conform to the following five points:

1. *Onset.* The onset is with pain before tumor is noticed or pathological fracture occurs. The patient may not consult his physician until the tumor appears, but in that case careful questioning will bring out the history of previous pain, perhaps intermittent in character. History of preceding trauma is frequent but always open to the question of whether the trauma caused the lesion or only called attention to it. Pathological fracture is common as the first symptom in carcinomatous metastases or in benign central lesions as cysts and giant cell tumors, but so rare as to be merely the exception which makes the rule in osteogenic sarcoma. Late in the disease it is not very uncommon. *We may say therefore that unless pain precedes other symptoms we may suspect that the case is not one of osteogenic sarcoma.*

2. *Duration.* We rarely get a history of years. Not infrequently the symptoms have existed about a year before the patient seriously seeks medical advice, but it is very rare that a patient allows 2 years to elapse. On the other hand it is very unusual for a patient to seek advice before at least a month has elapsed. The pain is usually bearable at first. The earliest case which we know of had had pain for a little less than a month. In benign osteogenic tumors the history is usually of years.

*Therefore if the patient sought advice in less than a month or over a year from the onset of symptoms we may suspect that the case is not one of osteogenic sarcoma.*

3. *The general condition.* Apparently bone sarcoma does not arise in the unhealthy except after 50 in cases of Paget's disease of the skeleton. If the patient was in poor health at the onset, the probabilities favor the tumor being inflammatory—tuberculosis, syphilis, osteitis, etc. Bone sarcoma seems to be a disease of the healthy, whose repair processes may be exuberant. This statement is not at variance with the belief of Ewing expressed to me in conversation, that

**Table 1.**

Criteria	Hubbard	Rixford	Wells	Bloodgood and Coley	Bloodgood	Bloodgood	Coley	Thompson	Coley	Bloodgood	Coley	586	Coley	183
Case number	29	50	64	100	101	102	172	184	261	408	501	586	Coley	183
History														
1. Onset with pain—not fracture or tumor	0	0	+	+	0	0	+	0	+	+		0	+	+
2. Duration. Not years or weeks but months	0	0	+	+	+	+	+	+	+	+		0	+	+
3. General condition—health at first	+	+	+	+	+	+	+	+	+	+		0	+	+
4. Age. Not over 50 unless Paget's	+	+	+	+	+	+	+	+	+	+		+	+	+
5. Rapid growth—month by month	+	0	+	+	+	+	+	+	+	+		0	+	+
Examination														
1. Immobility of soft parts	+	0	+	+	+		+	+	+	+		+	+	+
2. Location—certain bones rare	+	+	+	+	+	+	+	+	+	+		0	+	+
3. No inflammatory signs	+	+	0	+	0	+	+	+	+	+		+	+	0
4. Joint not affected	+	+	+	+	0		+		+	+		+	+	+
5. Size and shape (not pedunculated)	+	+	+	+	+	+	+	+	+	+		+	+	+
X-ray														
1. Both, central and subperiosteal—not either alone				+			+					+	+	+
2. Old shaft present—not expanded				+			+					0	+	+
3. Invasive—no rounded contours to spongy bone				+			+					+	+	+
4. Osteolytic and osteoblastic—not either alone.				+			+					+	+	+
5. Soft parts involved—at least extracortical				+			0					+	+	+
Microscopic														
1. Mitoses (hyperchromatism)	+	+	+	+	+	+	+	0	+	+	+	+	+	+
2. Pleomorphism	+	+	+	+	+	+	+	+	+	+	+	+	+	+
3. Tumor giant cells	+	+	+	+	0	+	+	+	+	+	+	+	+	+
4. Differentiation—partial	+	+	+	0	+	+	+	0	+	+	+	+	+	+
5. Tumor vessels	+	+		+	+	+	+	+	+	+	+	+	+	+
General														
1. Nature of pathological examination	+	0	0	+	+	0	+	+	+	0	0	+	+	0
2. Quality of data in general	0	0	+	+	0	0	+	0	+	+	0	+	+	+
3. Unanimity of specialists	+	+	+	+	0	+	+	0	+	0	0	0	+	+
4. The registry classification	+	+	+	+	+	+	+	+	+	+	+	+	+	+
5. The ultimate result	0	0	0	0	0	0	0	0	0	0	0	0	0	0

persons who develop bone sarcoma may have some essential defect in their mechanism for tissue repair. I believe myself that these patients “repair to death” as persons with hæmophilia “bleed to death.” That is that the mechanism which should check repair is absent or diminished, just as in persons with hæmophilia the clotting mechanism is abnormal. However, these sarcoma patients almost invariably appear to be in good health.

*Therefore unless the patient is considered in good health just before onset we may suspect the case is not one of osteogenic sarcoma.*

4. *Age.* With the exception of cases which also have Paget’s disease, 12 in number, we have no instances of osteogenic sarcoma in a patient over 50. Paget’s disease rarely occurs before 50. As recently computed by Bird and Sosman the incidence of osteogenic sarcoma in Paget’s disease is 12 to 14 per cent (personal communication). In the recent Survey of bone sarcoma cases in Massachusetts the writer concluded that the incidence of bone sarcoma is about 1 to 100,000 in the population at one time.

*Therefore in any patient over 50 who does not have coincident Paget’s disease we may suspect the case is not one of osteogenic sarcoma.*

5. *Rapidity of growth.* Benign osteogenic tumors (N.B. this does not mean benign giant cell tumor) may be exceedingly slow in growth, the change not even being noticeable from year to year; they may, however, have periods of increase of growth but this is seldom rapid enough to be noticeable month by month—rather year by year. Inflammatory conditions often noticeably enlarge day by day and very often week by week. Osteogenic sarcomata as a rule show steady enlargement practically always noticeable in a month.

*Therefore we may suspect that a case is not one of osteogenic sarcoma if the enlargement has been noticeable day by day or week by week or has not been noticeable month by month.* This statement of course excludes cases subjected to the modern therapeutic test of radiation.

## Examination

Cases of osteogenic sarcoma nearly always conform to the following five points in examination.

1. *Immobility of soft parts.* Of course, this is a difficult point to determine but one in which experience readily teaches. Rarely does an osteogenic sarcoma permit one to feel the soft tissues roll over the bone as does a giant cell tumor or cyst. This point is reversed in the inflammatory conditions which when they have perforated the bone may cause as much or more fixation of the soft parts than osteogenic sarcoma. Under the microscope there is a marked increase of large vessels in the periphery about an

osteogenic sarcoma. There are often huge dilated superficial veins. I believe this peculiar fixation of the soft parts may be due to the ramifications of these new vessels.

*Therefore we may suspect that a case is not one of osteogenic sarcoma if there is clearly mobility of the soft parts over the tumor.*

2. *Location.* Approximately one-half of all osteogenic sarcomata occur in the femur; one-quarter in the tibia; one-half of the remainder in the other long bones. Of the other bones in the skeleton the phalanges of fingers and toes, the carpal and most of the smaller tarsal bones appear to be exempt. Osteogenic sarcoma is rare in the shaft of a long bone, but this situation is the customary one for Ewing’s tumor or for carcinomatous metastases and myeloma.

*Therefore the situation of a tumor may make us suspect that it is not an osteogenic sarcoma if it is not in one of the known usual sites; and the suspicion is in inverse proportion to the frequency of occurrence at its site.*

3. *Inflammatory signs.* In exceptional cases the usual signs of inflammation may occur in osteogenic sarcoma; they are not at all unusual in cases of Ewing’s tumor. Radiation may temporarily produce them. However, the typical osteogenic sarcoma does not present, especially in its early stages, pronounced fever, tenderness, redness, leucocytosis, etc. Nevertheless these cases are usually mistaken for osteomyelitis.

*Therefore unless the signs of inflammation are absent or very mild we may suspect that the case is not one of osteogenic sarcoma.*

4. *Condition of neighboring joints.* The dissection of specimens of osteogenic sarcoma shows that it rarely invades the neighboring joints until late in the course of the disease or unless as a sequence to fracture or operation. Joint cartilage seems to act as a barrier to both benign giant cell tumor and osteogenic sarcoma. The latter almost invariably proceeds actually to the cartilage while the former often leaves a considerable amount of spongy bone between it and the cartilage. The presence of an osteogenic sarcoma near a joint does not involve the motion of the joint except in proportion to the fixation of the soft parts. Such limitation as there is is not due to spasm as is the case in inflammatory conditions of the joint or peri-articular structures (unless there is fracture also).

*Therefore in a case in which there is not a considerable degree of free motion in the adjacent joints we may suspect that the tumor is not an osteogenic sarcoma.*

5. *Size and shape.* No early sarcoma of small size nor of distinctly pedunculated shape has yet been registered. The facts that they are usually well developed when first noticed, that they usually surround the bone or most of its circumference; that they are as a rule both intracortical and extracortical, that they grossly resemble callus, make the writer feel that it is almost absurd to suppose that they start



in small areas and then spread. They can better be understood as starting in a region as callus does than in small groups of cells. If the latter why should they grow through the strong cortex to the other side no matter which side they start on? At any rate thus far all gross specimens show tumors of considerable size which are both medullary and subperiosteal with the old cortex more or less firmly in its old place. Pedunculated bone tumors are nearly always benign except when congenital exostoses have been excited by trauma to efforts at repair.

*Therefore if a tumor is not of considerable size or if it is pedunculated we may suspect it is not an osteogenic sarcoma.*

## The X-ray

The X-ray also furnishes us with five pretty constant criteria.

1. *Combined central and subperiosteal involvement.* Good roentgenographic pictures of osteogenic sarcomata demonstrate this point almost as well as sagittal gross sections. One must bear in mind, however, that superimposed bone outside the cortex may make the medullary shadow irregular in density. The little cuff of reactive bone of trumpet shape which surrounds the upper limit of the tumor appears in the X-ray as a triangular space on each side of the shaft under the uplifted periosteal edge. The presence of this is a sure indication of subperiosteal extracortical involvement. It represents the last line of defense of normal osteoblasts retreating in circular formation as the tumor advances under the periosteum. Unfortunately, the same phenomenon sometimes occurs as a defense against inflammation so that this reactive triangle in itself is not diagnostic of sarcoma. Benign tumors are either inside or outside the old cortex. Malignant are both.

*We may therefore suspect that it is not a case of osteogenic sarcoma when the X-ray does not show both medullary and subperiosteal involvement.*

2. *Presence of old shaft.* As stated above we rarely dissect a specimen of osteogenic sarcoma without finding the old shaft in its normal position—even if it is in fragments. It may be almost entirely destroyed in old tumors, but even then the remaining fragments are seldom pushed much out of place. The contrary takes place in benign giant cell tumor which gives the appearance of distending the bone. In Ewing's tumor the cortex is usually widened by the thrust of the tumor cells between the lamellæ, and old bone may be carried somewhat to the periphery. In osteogenic sarcoma the perforation of the cortex seems to be as a rule transverse from within outward radially through the cortex, or perhaps in the opposite direction. We have no clue as to whether they start inside or outside the cortex. If

new bone forms it follows these radiating lines. One must think of these radiating lines not as they show in the X-ray as spicules but as they really are in the gross specimen as ridges or osteophytes of irregular form on the surface of the cortex.

*Therefore if the X-ray does not show the old cortex or fragments of it in normal position, we should suspect that the case is not one of osteogenic sarcoma.*

3. *Invasive character.* Dissection shows and so do our standard series of osteogenic sarcomata that the advancing edge of these tumors in the spongy bone is practically never rounded and smooth as is nearly always the case in giant cell tumors and some vascular carcinomatous metastases. Osteogenic sarcoma advances by invasion of the cells and the margin is irregular. Giant cell tumors and a few vascular metastases advance by pressure atrophy due to their pulsation as do aneurysms.

*Therefore a sharp outline of the tumor against spongy bone may make us suspect that we are not dealing with an osteogenic sarcoma.*

4. *Osteolytic or osteoblastic or both.* A typical X-ray of a case of osteogenic sarcoma shows that the tumor is both osteolytic and osteoblastic. However, in rare cases, particularly if far advanced, these tumors may be only osteolytic or only osteoblastic. If wholly osteolytic the suspicion of metastatic carcinoma is aroused and if wholly osteoblastic of a benign osteogenic tumor. In most cases characteristic radiating spicules are shown and form a very positive sign, although exceptionally metastases or inflammation may produce them. The frequency of this sign of spicule formation is not enough to form a rule and the absence of it is not very strong evidence against osteogenic sarcoma.

*Therefore unless the X-ray shows that the tumor is both osteolytic and osteoblastic or if it shows that it is wholly one or the other, suspicion that it is not a case of osteogenic sarcoma is aroused.*

5. *Involvement of soft parts.* This is a difficult point on which to interpret the X-ray. Giant cell tumors which have burst their capsule have frequently been interpreted as having the soft parts involved, and yet dissection in such cases has never shown this form of tumor as actually invading the soft parts although it may push them aside on fascial planes. Vice versa, the X-ray of an osteogenic sarcoma may lead us to think it has not involved the soft parts and dissection will show that it has. If we define the "soft parts" as including the extracortical space between the raised periosteum and the bone as shown by the "reactive triangle" above alluded to at its upper limit, we may get much help. Dissection shows that when we find this condition the tumor is always at least subperiosteal and usually has also broken through the periosteum and begun to invade the soft parts.

*Therefore we may say that a tumor which does not show in the X-ray either invasion of the soft parts or the reactive triangle is perhaps not an osteogenic sarcoma.*

## Microscopic Criteria

The microscope gives also 5 pretty definite criteria common to most osteogenic sarcomata.

**1. Mitoses and hyperchromatism.** The relative frequency of mitotic figures has long been a guide in estimating malignancy in all tumors. Rapid growth in most tissues is characterized by a relatively large number of mitoses. Like other criteria this one has its exceptions for numerous mitoses may occur for instance in fungating granulation tissue and also in certain benign tumors. In benign giant cell tumor for instance they are often quite numerous and if an operation has been done and the wound is fungating they are usually very numerous. On the other hand excess of mitotic figures is a very constant finding in typical osteogenic sarcoma. Hyperchromatism of nuclei is a parallel phenomenon probably equivalent to mitotic activity or at least indicative of it. Sometimes it is seen without it and yet it indicates it.

*Therefore the finding of numerous mitoses in a bone tumor does not necessarily indicate osteogenic sarcoma, but absence or infrequency of mitotic figures should arouse the suspicion that the case is not one of osteogenic sarcoma.*

**2. Pleomorphism.** All our instances of osteogenic sarcoma which have run a malignant course, showed this criterion constantly. The degree of pleomorphism is of course a matter of individual judgment. There is a normal range of variations of size and shape in normal cells which it requires experience to recognize. In some cells the range is great, for instance the endothelial leucocyte is protean in, its ability to change in shape and size. In general a bone tumor must be considered within normal limits of pleomorphism if no cells are found which cannot be duplicated in normal inflammation. This is the rule in benign giant cell tumors for none of the 100 standard tumors of this kind in the Registry series contain even small numbers of distinctly atypical cells. On the other hand our series of osteogenic sarcomata all do. Ewing's tumors are not pleomorphic and yet are very malignant.

Probably the best single way in which to grade osteogenic sarcomata would be to base the prognosis on the degree of pleomorphism. This is equivalent to expert histologic opinion, for any good histologist probably bases his opinion of the prognosis in any malignant tumor largely on its pleomorphism, although he takes account of the other factors as mitotic activity, hyperchromatism and the arrangement of chromatin, nucleus and nucleolus.

However, it does not yet appear necessary to attempt to grade osteogenic sarcoma, for our collection is not yet large enough and as yet we cannot say bad, worse, worst. To say Bad is enough, for after 5 years search we find only 13 cures.

*Therefore any bone tumor which does not show pleomorphism is probably not an osteogenic sarcoma.*

**3. Tumor giant cells.** It is not difficult to demonstrate to a student the difference between typical tumor giant cells and foreign body giant cells. However, occasional doubtful giant cells are found, but very rarely are all the giant cells in a single slide doubtful. A few individual giant cells or small areas of foreign body giant cells are of frequent occurrence in osteogenic sarcomata, and have little significance in diagnosis, as they probably merely indicate hæmorrhage in the tumor. On the other hand one may confidently expect a tumor to be malignant if it contains tumor giant cells but not necessarily to be a primary bone tumor. Tumor giant cells may occur in cancer also but we seldom see them in bone metastases. Then, too, many osteogenic sarcomata show no tumor giant cells.

*This criterion therefore is not universal, but we may say that its presence in an osteogenic tumor is a very reliable sign of malignancy; but its absence need not make one suspicious either of the malignancy of the tumor or of its place in the osteogenic series.*

**4. Differentiation.** It has proved impossible to make the differentiation toward intercellular substances as fibro-chondro-osteo-criteria of malignancy. There is an endless variety of proportions of these intercellular substances and an imperceptible series of gradations from one intercellular substance to another. At most, differentiation can only be used as a criterion of degree, the less the differentiation, in other words the more cellular the tumor, the more malignant. And now that radiation has been shown to be effective in the inverse way it is still harder to use this factor as a criterion. For instance Ewing's tumor which may be simply an undifferentiated form of osteogenic sarcoma has nowadays with radiation a better prognosis than a relatively well differentiated osteogenic sarcoma of the chondro-type. Yet the relative proportion of cellular tissue in chondromatous tumors is very important in their prognosis, for the greater it is the worse the prognosis.

*Therefore in an osteogenic tumor very complete differentiation or almost no differentiation is better than incomplete differentiation, and the evidence of quite complete differentiation should make us suspect that the case is not an osteogenic sarcoma, but a benign osteogenic tumor.*

**5. Tumor vessels (vascular arrangement).** As this criterion is my own hobby I hesitate to present it but as I have found it very reliable even if new, I offer it for it may help others. Early in the Registry work I noticed that the malignant tumors had a different vascular arrangement

from the benign giant cell tumors. The latter have only capillaries or sinuses without any walls except the endothelium lining them. As a contrast to this all malignant tumors have definite branching vessels with walls of varying thickness largely composed of tumor cells. In other words these tumors have a perithelial arrangement as a constant factor, and the vessels branch like the limbs or twigs on a tree. The tumor cells hang on them like swarms of bees, whether the cells have no intercellular substance as in Ewing's tumors or well developed cartilaginous material as in some "chondrosarcomata." One may see an endothelial lining or perhaps a lining of tumor cells, and immediately adjacent perithelial arrangements of cartilage cells. Great variety of appearance of these tumor vessels is a characteristic also.

I find these tumor vessels a constant factor. They are certainly useful in distinguishing giant cell tumors from the osteogenic tumors, benign and malignant. As a criterion to differentiate malignant from benign osteogenic tumors or callus it again becomes a question of the individual cells forming the walls. Benign osteogenic tumors do not have pleomorphic cells in the vessel walls. I made one error in considering exuberant callus malignant, on account of somewhat atypical vessels.

*My personal conviction is that every osteogenic sarcoma shows tumor vessels and that a tumor which does not show them in several sections is not an osteogenic sarcoma.*

Experienced pathologists have, of course, noticed these vessels as the vascular arrangement of tumors in general, but so far as I know they have not contrasted this vascular arrangement with the interstitial blood supply of giant cell tumors. Perhaps "vascular arrangement" is a better heading than "tumor vessels" which I have used hitherto.

## General Criteria

There are five general criteria of malignancy in a bone tumor which seem to me important.

1. *The nature of the pathological examination.* For instance the most expert pathologist will not be able to give us as much help on the stingy bit of dried tissue handed him by some uninterested operator, as can a keen surgeon in an out-of-the-way clinic who has made a complete and careful examination and description of the amputated limb. Opinion based on careful examination of the dissected gross specimen by a competent pathologist or by a good surgical observer is very strong evidence for osteogenic sarcoma. Yet it is by no means absolute.

We have two gross specimens in the Registry Collection which have not yet been satisfactorily classified. For example, Case 187 which is claimed as a cured case of

osteogenic sarcoma by Ewing and Coley, I have not included in the present list although Dr. Ewing examined the gross specimen and still possesses it. From the situation of the tumor in the lower end of the radius and from Dr. Ewing's own description, I suspect it to be a variant of giant cell tumor.

*Nevertheless we may say that if the diagnosis is confirmed by competent examination of the gross specimen it is one of the strongest but not an absolute criterion. If other important criteria do not agree, the suspicion is aroused that the tumor is not an osteogenic sarcoma. Furthermore histological reports even by excellent pathologists on small and imperfect exploratory specimens should not be accepted unless in agreement with other important criteria.*

2. *The quality of the data.* What has been said in regard to the character of the pathological data applies to the other data. A history taken by someone interested in the patient or in the bone sarcoma problem is likely to be much more fruitful than if carelessly taken by someone interested in neither. Our best histories have come from either the small hospitals where the patient is of paramount interest or from the occasional man in some large clinic who is interested in bone tumors.

The character of the roentgen data is of great importance. There is a deplorable tendency to neglect technique in bone cases. The greatest possible detail is needed and if attained, may be of more importance to the patient than the surgeon's knife. Undoubtedly we must look to the roentgenologist to find the criteria of diagnosis at the early stage when pain has begun and tumor has not yet appeared.

*We may say then that the quality of the data has much to do with our conviction of the diagnosis of osteogenic sarcoma.*

3. *Unanimity of the different specialists.* In typical instances of osteogenic sarcoma the clinician, the roentgenologist, the operator, and the pathologist all arrive independently at the same diagnosis. As our experience progresses and knowledge diffuses, this rule becomes more striking.

A patient entering a hospital which has cooperated in the work of the Registry will probably have his bone tumor independently diagnosed by the different departments. If one has doubt, all should have and probably actually have. General agreement however will be the rule.

*To express this differently, any hospital which is doing its best for cases of bone tumor will promptly diagnose the majority of cases of osteogenic sarcoma independently in each department concerned and the synthesis of these opinions and the action to be taken on them will be the responsibility of someone familiar with the work of the Registry.*

4. *The Registry classification.* A criterion of more or less value in regard to the diagnosis of a case of osteogenic



sarcoma is whether or not it has been so accepted by the Registry Committee. This is neither final nor fundamental and merely represents the best obtainable collection of opinions on such data as is furnished at a given date. Any hunter knows the difficulty of distinguishing game running through the woods. An idea of the height of the animal is obtained at one glance, the flash of a white tail at another, and the outline of horns at a third. The conviction that a deer has passed may be arrived at, but the story the hunter tells will be believed in proportion to his own experience and standing in intellectual honesty. At that, he may be mistaken.

*Expert opinion would not be expert opinion if as a rule it were capable of proof. The relative importance of the criterion of the Registry Classification is of this degree and varies with the character of the data and of the Committee.*

The entity of osteogenic sarcoma has been recognized by a group, as hunters recognize a rare animal by repeated glimpses in all degrees of perfection, from a flash through the woods to the slaughtered, dissected, stuffed, macerated, dried, bottled, or serially sectioned individual. One hunter who might recognize the fossil vertebræ of the animal might not recognize the living creature darting through the woods. The practical hunter would, although he might confuse it with one of an allied species. The Registry Committee has had the advantage of being aided by much expert help and by varied points of view from different individuals. It has succeeded in establishing this entity and describing its characteristics but in individual cases it may be mistaken on fleeting glimpses. The 13 cases here submitted are of this character. It is our belief that they were instances of osteogenic sarcoma, but we ourselves recognize the possibility of error.

In our series of 200 standard osteogenic sarcomata nearly 50 per cent are still living under the 5 year limit. We feel much more sure of the correctness of diagnosis in most of these cases than in the 13, although in many much of the outline was behind the trees.

**5. The ultimate result.** It is easy to say that the Committee modify their diagnoses when they know the result. This is true; we do, so far as we can, but in many cases we do not yet know the result. We have also been criticized for letting each expert see the opinions of those given before him. We are in fact glad to have him do so. We want every bit of information and advice we can get, and so should every expert. It can do no harm, for we realize that on such data as we get, this writing of opinions is often merely an amusing mental exercise.

To be sure there is a serious side when we think of how many unregistered cases of bone sarcoma do not even get the benefit of the opinion of the Registrar which is freely given for rich or poor and always should be. In our hospitals, decisions in cases of bone sarcoma are often

made on less experience than that which even a newly appointed Registrar would have at his command. Very few pathologists or surgeons see 10 cases of this lesion in their whole professional careers, where the diagnosis is definite and the outcome known. A new Registrar who has studied this series of 650 cases could certainly be of help to anyone on whom the responsibility of decision of life and limb rests.

*But we must confess that even the most experienced after the study of all the 650 registered cases must sometimes modify his diagnosis by the ultimate result. If a case diagnosed as osteogenic sarcoma does not die within 5 years with metastases in the lungs all criteria should again be scrutinized with the greatest care.*

## **Part II.—The 13 Cases of 5-year Cures of Osteogenic Sarcoma**

As most of these cases have already appeared in the literature I will merely give references and discuss a few points in each.

**CASE 29.** This case has never been published in detail. It was that of a boy of 14 with a tumor of the upper end of the tibia. He was the nephew of an able surgeon who recognized the seriousness of the lesion within 6 weeks of onset and promptly did a thigh amputation. It is perhaps the record for prompt diagnosis and treatment. The patient has been well for 9 years. An interesting feature of this case was that postoperative treatment was conducted by Dr. James B. Murphy of the Rockefeller Institute on his theory derived from experiments in animals that a mild lymphocytosis repeatedly aroused by light, diffuse doses of the roentgen ray prevents experimental inoculation of tumors in animals and, therefore, might prevent the growth of small metastases in the human being.

There are several of our criteria lacking in this case, for instance the onset was with trauma not pain; the history a matter of weeks rather than months; no X-rays or gross specimen have been preserved; the hyperchromatism is not great nor are single mitoses very frequent. In fact the diagnosis is largely based on the extreme pleomorphism of the cells, the presence of many typical tumor giant cells with multiple mitoses and Dr. Mallory's original written report on the gross specimen. There is general agreement among the pathologists.

**CASE 50.** See Binnie's *Surgery*, vol. iii, p. 456.

This was a man of 44 with a very large tumor of the lower end of the femur. The case lacks some very important criteria. The age, 44, was exceptional. There was little pain, and tumor was the first symptom. The tumor had been present 3 years at least. It had differentiated largely to cartilage and bone, and there was little cellular tissue.

**Table 2.** Five year cures—thirteen cases

Case	Reg'st'd by	Name	Age	Bone	Previous partial ops.	Date amp.	Date last report	Toxins	Radiation	Reported in
29	Hubbard	S.	14	Tibia	0	6-23-16	June, 1925	0	0	Never reported
50	Rixford	O.	44	Femur	0	1-22-09	Oct., 1924	0	0	Binnie's Surgery, vol. iii, p. 456
64	Wells	B.	19	Femur	+	8-5-09	June, 1925	0	0	Surg., Gynec. & Obst, 1922, May, p. 698
100	Bloodgood & Coley	P.	23	Femur	+	Aug., '17	April, 1925	+	+	To be reported by Coley
101	Bloodgood	N.T.	24	Femur	0	7-8-13	May 16, '24	0	0	J. Radiol., 1920, Mar., p. 149
102	Bloodgood	B.	11	Tibia	+	May, '13	April, 1925	?	?	J. Radiol., 1920, Mar., p. 148
172	Coley	S.	19	Femur	?	Aug., '20	April, 1925	+	+	To be reported by Coley
184	Coley	T.	26	Femur	0	8-20-16	Jan., 1924	+	+	To be reported by Coley
261	Thompson	M.	11	Femur	0	4-8-16	Oct., 1924	0	0	Surg. Clin. of North America, 1922, Oct.
408	Coley	D.	18	Femur	+	4-7-06	April, 1925	+	0	To be reported by Coley
501	Bloodgood	S.	?	Femur	+	1-18-13	June, 1924		?	Not reported
586	Coley	F.	48	Femur	+	10-31-16	April, 1925	+	+	To be reported by Coley
183	Coley	St.		Tibia		Not amputated		+	+	To be reported by Coley

There are no X-rays and no detailed description of the gross specimen. The diagnosis rests wholly on a few small areas which show a cellular growth with some mitotic activity and pleomorphism. Yet there is agreement among the pathologists on grading this as an osteogenic sarcoma rather than a benign or borderline chondroma. There are typical tumor giant cells.

The history, however, is strongly against this being a real case of osteogenic sarcoma. "Patient has always been well except as to his left knee on which 3 years ago he first noticed a small lump on the outer side; this, patient says, was movable. Patient indicated that this was at the summit of the external condyle of the left femur. He knows of no injury save a slight blow at this point received some weeks before the lump was noticed. The lump has grown pretty continuously ever since, although being stationary at times. It has never receded; has never been painful but was tender at one spot on the upper side of the patella. There is some tenderness in walking. Patient says that he has rather gained weight recently than lost."

Patients with osteogenic sarcoma of the femur do not usually walk 3 years without pain and gain weight. This is the exception which proves the rule unless the histological malignancy in this case is the exception which proves another rule.

CASE 64. This case was reported by Wells. Neither gross specimen nor X-ray was preserved. There were marked inflammatory signs. Repeated operations were done which might well have diffused metastases.

The diagnosis is based on expert opinion on the slides and is not strongly positive for most of the tissue is obviously inflammatory. While agreeing in the diagnosis, there is evident doubt among all the pathologists.

CASE 100. After two incomplete operations the thigh was amputated. She was also treated by Coley toxins and radiation.

This case fulfills all the criteria with the possible exception of differentiation. The tumor is so well differentiated that the sections closely resemble callus. Otherwise than this and the survival after so much surgery, the case seems a typical osteogenic sarcoma.

CASE 101. The questionable features in this case were of its inflammatory nature; onset by fixation of joint rather than pain; the presence of many of the signs of inflammation clinically and in the sections; involvement of joint. No X-ray is preserved and the character of the data is unsatisfactory. There is no agreement on classification among the pathologists except on the histological malignancy. There is a question whether the tumor does not belong in the myeloma series.

CASE 102. No X-ray is preserved. The data in general are unsatisfactory. There is no good gross description of specimen but the histology is pretty typical of osteogenic sarcoma.

CASE 172. The one favorable feature is Ewing's description of the amputated leg: "Shows early and unusually limited central and subperiosteal osteogenic sarcoma."

CASE 184. The sections resemble a very cellular osteitis fibrosa and some of the pathologists class it as such. The

Committee, however, feels that it should be classed as a sarcoma. Mitosis and hyper-chromatism are not marked and differentiation is pretty complete. We have no X-ray and in such a case the X-ray would mean much.

CASE 261. This case has every unfavorable character except that the tumor was pretty well confined beneath the periosteum and in the center of the bone. Histologically it was very malignant. Amputation was done without exploratory incision and there was no after treatment. It is in my opinion the most typical and also the most complete case in the series. It shows surgery at its best.

CASE 408. The character of the exploratory operation through the joint rendered the prognosis very unfavorable. We have no good report of the gross specimen or X-ray. However, there can be little doubt from the description of the operation and the histology that this was a malignant tumor. It hardly seems as if amputation alone could have cured in this case. No radiation was used according to our notes; the mixed toxins were used. Compare the preceding case in which no exploration was done or after treatment given.

Although the pathologists agree that this case was malignant the histology is unsatisfactory for classification.

CASE 501. The notes on this case are very inadequate. There is no real history, no X-ray, and the histology is barely adequate to include it in this group. Several pathologists have raised the question of its being a giant cell tumor. Complete data, even one good X-ray, would probably expel all doubt.

CASE 586. This case is well registered with X-rays, photos, and slides but it is really not one of the true osteogenic sarcomata. "Had fractured femur at 4 and 11. At 21 had slight periostitis at site of fracture." In August, 1916, when 48 years old, he had a tumor of the femur at the site of one of the fractures. He was treated by curettage, X-ray, radium, and toxins for several months, and the thigh amputated October, 1916. Wellin April, 1925. There was a fairly circumscribed mass at the site of the fracture and an open granulating wound over it. Histologically it is a sarcoma. There is doubt among the pathologists as to whether it should be classed as an osteogenic sarcoma at all or as a fibrosarcoma arising in scar tissue.

CASE 183. This case is the only one in which amputation did not contribute to the success which must have been due to radiation or toxins or both. It has been and will be again reported by Dr. Coley in full. It is a unique, remarkably encouraging case, for the limb was saved and metastases in the glands of the groin receded and did not reappear. Logically the mixed toxins and radiation must share the credit. There is an almost equally brilliant case, 267, among the Ewing tumors, also treated by radiation and toxins.

## Summary

One must realize that the cases here presented are by no means the only possible 5 year cures of osteogenic sarcomata in the Registry series. It would be better to say that they are the 13 most authentic ones. Other cases especially Case 187 should perhaps also be included and discussed, but there is a limit to interest in the subject if too doubtful instances are brought into question.

I have done my best to be judicial in selecting these, and my colleagues, Doctors Bloodgood and Ewing, have agreed with me that these are the best representatives of cured osteogenic sarcomata and even these are pretty doubtful. If it had not been for Coley's enthusiasm and optimism we should have few to record. Coley has shown us at least that cases considered hopeless may be cured. Even if the hopelessness was due in some cases to the errors of pathologists in mistaking benign tumors for malignant ones, Coley's optimism has been well justified. Whether or not the evidence also justifies his faith in the use of mixed toxins is an academic matter compared with the bald facts that he can furnish evidence of the cure of *apparently* hopeless cases, and that he has furnished evidence of nearly as many cures as all the other surgeons of the country together. He has also furnished evidence of more cures than shown in the above list but some of these other cases are considered by our Committee to be instances of benign giant cell tumor.

From a logical standpoint it seems to me that argument as to the value of the toxins should rest on their postoperative use, for the fact is that over one-half of the successful cases following amputation have had the postoperative use of this agent. To be sure there are few in all.

Further evidence of the value of the mixed toxins will appear in Conner's paper on Ewing's tumor in the *Archives of Surgery*, but as in these cases there was confusion owing to coincident use of radiation.

Of the present series of 13, in 5 cases amputation must be given the credit alone, unless the Murphy method of diffuse X-ray is claimed to share one of these (Case 29). This idea of Murphy's seems to me to deserve more extended trial.

In two other cases (102 and 501), we do not know whether the toxins were used or not.

In 5 cases they were used before or after operation but in only one of these was radiation not used also.

Finally, in 1 case the cure must be credited to either toxins or radium or both. This case was unique in many respects but clearly histologically malignant.

Another point brought out is interesting. In only 5 cases was the amputation done at the same time as the exploration. In the other 7, exploration was done at least once and in some cases several times before amputation. Even if

done only once it was done in a manner which should have caused diffusion of the tumor.

In only 1 case was the amputation done without preliminary incision *but this was the most typical malignant case.*

These facts speak in two ways, either against the malignancy of these particular tumors or in favor of exploration being a harmless procedure.

I have presented what I believe to be the best evidence of 5 year cures so far collected by the Registry. We can continue to guess on the strength of these meager facts or we can co-operate to collect a more complete series.

Shall the College continue the Registry of Bone Sarcoma?